HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BETOPTIC S safely and effectively. See full prescribing information for BETOPTIC S.

BETOPTIC S (betaxolol hydrochloride) suspension for ophthalmic use
Initial U.S. Approval: 1985

RECENT MAJOR CHANGES

Use in Specific Populations, Pediatric Use (8.4) 6/2007

INDICATIONS AND USAGE

BETOPTIC S® is a beta-adrenergic receptor inhibitor indicated for the treatment of elevated intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension (1).

DOSAGE AND ADMINISTRATION

- Instill one drop in the affected eye(s) twice daily (2)

DOSAGE FORMS AND STRENGTHS

- Bottles filled with 2.5, 5, 10, and 15 mL of 0.25% sterile ophthalmic suspension (3)

CONTRAINDICATIONS

- Hypersensitivity to any component of this product (4)
- Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, and cardiogenic shock (4)

WARNINGS AND PRECAUTIONS

- Same adverse reactions found with systemic administration of beta-adrenergic receptor inhibitors may occur with topical ophthalmic administration (5.1).
- Beta-adrenergic receptor inhibitors may mask the signs and symptoms of acute hypoglycemia and should be administered with caution in diabetic patients subject to hypoglycemia (5.3).
- Beta-adrenergic receptor inhibitors may mask certain clinical signs (e.g. tachycardia) or hyperthyroidism (5.4).

ADVERSE REACTIONS

The most frequent adverse reaction is transient ocular discomfort (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 and or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Oral beta-adrenergic receptor inhibitors may have additive effects (7.1)
- Catecholamine-depleting drugs may have additive effects (7.2)
- Concomitant adrenergic psychotropic drugs may have additive effects (7.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2008

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BETOPTIC S® Ophthalmic Suspension 0.25% is indicated for the treatment of elevated intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

Instill one drop of BETOPTIC S® Ophthalmic Suspension 0.25% in the affected eyes twice daily. It may be used alone or in combination with other intraocular pressure lowering medications.

3 DOSAGE FORMS AND STRENGTHS

Bottle filled with 2.5, 5, 10, and 15 mL of 0.25% sterile ophthalmic suspension

4 CONTRAINDICATIONS

BETOPTIC S® Suspension is contraindicated in patients with:

- sinus bradycardia
- greater than a first degree atrioventricular block
- cardiogenic shock
- patients with overt cardiac failure
- hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 General

As with many topically applied ophthalmic drugs, this drug is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic receptor inhibitors may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and death due to cardiac failure, have been reported with topical application of beta-adrenergic receptor inhibitors.

5.2 Cardiac Failure

BETOPTIC S® Suspension has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC S® should be discontinued at the first signs of cardiac failure.

5.3 Diabetes Mellitus

Beta-adrenergic receptor inhibitors should be administered with caution in patients subject to hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor inhibitors may mask the signs and symptoms of acute hypoglycemia.

5.4 Thyrotoxicosis

Beta-adrenergic receptor inhibitors may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic receptor inhibitors, which might precipitate a thyroid storm.

5.5 Muscle Weakness

Beta-adrenergic receptor inhibitors have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

5.6 Surgical Anesthesia

The necessity or desirability of withdrawal of beta-adrenergic receptor inhibitors prior to major surgery is controversial. Beta-adrenergic receptor inhibitors impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor inhibitors have experienced protracted, severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. In patients undergoing elective surgery, consider gradual withdrawal of beta-adrenergic receptor inhibitors. If necessary during surgery, the effects of beta-adrenergic receptor inhibitors may be reversed by sufficient doses of adrenergic agonists.

5.7 Bronchospasm and Obstructive Pulmonary Disease
Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although re-challenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta-adrenergic receptor inhibitors cannot be ruled out.

5.8 Atopy/Anaphylaxis
While taking beta-adrenergic receptor inhibitors, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.9 Angle-Closure Glaucoma
In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle. This may require constricting the pupil. Betaxolol has little or no effect on the pupil and should not be used alone in the treatment of angle-closure glaucoma.

5.10 Cerebrovascular Insufficiency
Because of potential effects of beta-adrenergic receptor inhibitors on blood pressure and pulse, these inhibitors should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with BETOPTIC S®, alternative therapy should be considered.

5.11 Bacterial Keratitis
Bacterial keratitis may occur with use of multiple dose containers of topical ophthalmic products when these containers are inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. Instruct patients on appropriate instillation techniques. [see *Patient Counseling Information (17)*].

5.12 Choroidal Detachment
Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In clinical trials, the most frequent adverse reaction associated with the use of BETOPTIC S® Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other adverse reactions have been reported in small numbers of patients:
Ocular: blurred vision, corneal punctuate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes.
Systemic adverse reactions include:
Cardiovascular: Bradycardia, heart block and congestive failure.
Pulmonary: Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure.
Central Nervous System: Insomnia, dizziness, vertigo, headaches, depression, lethargy, and increase in signs and symptoms of myasthenia gravis.
Other: Hives, toxic epidermal necrolysis, hair loss and glossitis. Perversions of taste and smell have been reported.
In a 3-month, double-masked, active-controlled, multicenter study in pediatric patients, the adverse reaction profile of BETOPTIC S® Ophthalmic Suspension 0.25% was comparable to that seen in adult patients.

6.2 Additional Potential Adverse Reactions Associated with Betaxolol
Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, corneal punctuate staining which may appear in dendritic formations, edema and anisocoria.

7 DRUG INTERACTIONS

7.1 Oral Beta-Adrenergic Receptor Inhibitors
Patients who are receiving a beta-adrenergic receptor inhibitor orally and BETOPTIC S® Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

7.2 Catecholamine-Depleting Drugs
Close observation of the patient is recommended when a beta-adrenergic receptor inhibitor is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia which may result in vertigo, syncope, or postural hypotension.

7.3 Concomitant Adrenergic Psychotropic Drugs
Betaxolol is an adrenergic receptor inhibitor; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic effects
Pregnancy Category C: Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women.

BETOPTIC S® Ophthalmic Suspension 0.25% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S® Ophthalmic Suspension 0.25% is administered to nursing women.

8.4 Pediatric Use

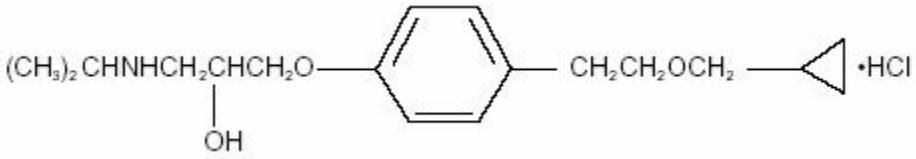
Safety and IOP-lowering effect of BETOPTIC S® Ophthalmic Suspension 0.25% has been demonstrated in pediatric patients in a 3-month, multicenter, double-masked, active-controlled trial.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

10 OVERDOSAGE
No information is available on overdosage of humans. The oral LD_{50} of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor inhibitor are bradycardia, hypotension and acute cardiac failure.

A topical overdose of BETOPTIC S® Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

11 DESCRIPTION
BETOPTIC S® Ophthalmic Suspension 0.25% contains betaxolol hydrochloride, a cardioselective beta-adrenergic receptor inhibitor, in a sterile resin suspension formulation. Betaxolol hydrochloride is a white, crystalline powder, with a molecular weight of 343.89. The chemical structure is presented below.



Empirical Formula:
$C_{18}H_{29}NO_3$•HCl
Chemical Name:
(±)-1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride.

Each mL of BETOPTIC S® Ophthalmic Suspension 0.25% contains: **Active:** betaxolol HCl 2.8 mg equivalent to 2.5 mg of betaxolol base. **Preservative:** benzalkonium chloride 0.01%. **Inactives:** mannitol, poly(styrene-divinyl benzene) sulfonic acid, carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.
BETOPTIC S® Ophthalmic Suspension 0.25% has a pH of approximately 7.6 and an osmolality of approximately 290 mOsmol/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Betaxolol HCl, a cardioselective (beta-1-adrenergic) receptor inhibitor, does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action. Orally administered beta-adrenergic receptor inhibitors reduce cardiac output in healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor antagonists may inhibit the sympathetic stimulatory effect necessary to maintain adequate cardiac function.

When instilled in the eye, BETOPTIC S® Ophthalmic Suspension 0.25% has the action of reducing elevated intraocular pressure, whether or not accompanied by glaucoma. Ophthalmic betaxolol has minimal effect on pulmonary and cardiovascular parameters.

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Betaxolol has the action of reducing elevated as well as normal intraocular pressure and the mechanism of ocular hypotensive action appears to be a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry.

12.2 Pharmacodynamics

The onset of action with betaxolol can generally be noted within 30 minutes and the maximum effect can usually be detected 2 hours after topical administration. A single dose provides a 12-hour reduction in intraocular pressure. In some patients, the intraocular pressure lowering responses to BETOPTIC S® may require a few weeks to stabilize. As with any new medication, careful monitoring of patients is advised.

Ophthalmic betaxolol solution at 1% (one drop in each eye) was compared to placebo in a crossover study challenging nine patients with reactive airway disease. Betaxolol HCl had no significant effect on pulmonary function as measured by Forced Expiratory Volume in one second (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC and was not significantly different from placebo. The action of isoproterenol, a beta stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol.

No evidence of cardiovascular beta adrenergic-blockade during exercise was observed with betaxolol in a double-masked, crossover study in 24 normal subjects comparing ophthalmic betaxolol and placebo for effects on blood pressure and heart rate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested.

In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic.

14 CLINICAL STUDIES

In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of BETOPTIC S® Ophthalmic Suspension 0.25% and BETOPTIC® Ophthalmic Solution 0.5% were clinically equivalent. BETOPTIC S® Suspension was significantly more comfortable than BETOPTIC® Solution.

16 HOW SUPPLIED/STORAGE AND HANDLING

BETOPTIC S® Ophthalmic Suspension 0.25% is supplied as follows: 2.5, 5, 10 and 15 mL in plastic ophthalmic DROP-TAINER® dispensers. Tamper evidence is provided with a shrink band around the closure and neck area of the DROP-TAINER package.

2.5 mL: **NDC** 0065-0246-20
5 mL: **NDC** 0065-0246-05
10 mL: **NDC** 0065-0246-10
15 mL: **NDC** 0065-0246-15

Storage and Handling

Store upright at 2° - 25°C (36° - 77°F).

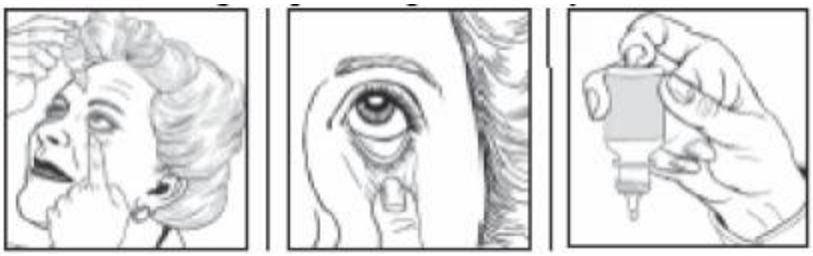
Shake well before using.

17 PATIENT COUNSELING INFORMATION

How to Use The DROP-TAINER® Bottle

The DROP-TAINER® bottle is designed to assure the delivery of a precise dose of medication. Before using your DROP-TAINER®, read the complete instructions carefully.

1. If you use other topically applied ophthalmic medications, they should be administered at least 10 minutes before BETOPTIC S®.
2. Wash hands before each use.
3. Before using the medication for the first time, be sure the Safety Seal on the bottle is unbroken.
4. Tear off the Safety Seal to break the seal.
5. Before each use, shake well and remove the screw cap.
6. Invert the bottle and hold the bottle between your thumb and middle finger, with the tips of the fingers pointing towards you.



7. Tilt your head back and position the bottle above the affected eye. DO NOT TOUCH THE EYE WITH THE TIP OF THE DROPPER.
8. With the opposite hand, place a finger under the eye. Gently pull down until a “V” pocket is made between your eye and lower lid.
9. With the hand holding the bottle, place your index finger on the bottom of the bottle. Push the bottom of the bottle to dispense one drop of medication. DO NOT SQUEEZE THE SIDES OF THE BOTTLE.
10. Repeat 6, 7, 8 and 9 with other eye if instructed to do so.
11. Replace screw cap by turning until firmly touching the bottle.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye(s) or surrounding structures. Patients should also be instructed that ocular solutions, if handled improperly, could become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye(s) and subsequent loss of vision may result from using contaminated solutions.

Patients should be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician’s advice concerning the continued use of the present multidose container.

Patients requiring concomitant topical ophthalmic medications should be instructed to administer these at least 10 minutes before instilling BETOPTIC S® Suspension.

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Alcon®
Alcon Laboratories, Inc.
Fort Worth, Texas 76134